10/530176

AU03/01296

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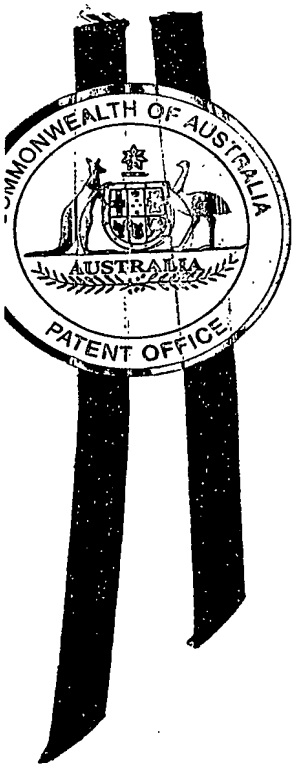

WITNESS my hand this
Thirteenth day of October 2003

J R Yabsley

JONNE YABSLEY
TEAM LEADER EXAMINATION
SUPPORT AND SALES

Our Ref: 7746770

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AUSTRALIA

Patents Act 1990

PROVISIONAL SPECIFICATION

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Invention Title: **Compositions and therapeutic methods involving platinum complexes**

The invention is described in the following statement:

COMPOSITIONS AND THERAPEUTIC METHODS INVOLVING PLATINUM COMPLEXES

Field of the Invention

This invention relates to compounds, compositions, methods and therapeutic uses involving, containing, comprising, including and/or for preparing platinum-isoflavonoid complexes and combination therapies involving platinum-based therapeutics together with isoflavones and analogues thereof.

Background

Platinum-based compounds find utility as pharmaceutical agents in chemotherapy. An important platinum-based compound is cisplatin (*cis*-diamminedichloroplatinum (II); *cis*-$Cl_2(NH_3)Pt$). Cisplatin has a square planar geometry, with each of the two chloride groups (and likewise, each of the two amine groups) being adjacent, or *cis*, to each other.

Cisplatin was first approved for human use in the late 1970's and is prescribed for the treatment of a variety of tumours including germ-cell, advanced bladder carcinoma, adrenal cortex carcinoma, breast, testicular and ovarian cancer, head and neck carcinoma and lung carcinoma.

Cisplatin is active against proliferating or cancerous cells by binding to DNA and interfering with its repair mechanism, eventually leading to cell death. It is thought that the first step in the cellular process is that a molecule of water replaces one of the chloride ions of cisplatin. The resulting intermediate structure can then bind to a single nitrogen on a DNA nucleotide. Following that, the second chloride is also replaced by another water molecule and the platinum agent then binds to a second nucleotide. Binding studies of cisplatin with DNA have indicated a preference for nitrogen 7 on two adjacent guanines on the same strand. It also binds to adenine and across strands to a lesser extent.

The binding of cisplatin to DNA causes production of intrastrand cross-links and formation of DNA adducts. The adducts or cisplatin-DNA complexes attract the attention of DNA repair proteins which become irreversibly bound. The resulting distortion to the shape of the DNA by the binding of cisplatin prevents effective repair and hence, cell death.

However, patients undergoing cancer chemotherapy often have to contend with quite severe and debilitating side effects due to the toxicity of the active agents. Common side effects of cisplatin therapy are nausea and vomiting. Other side effects include temporary reduction in bone marrow function, numbness or tingling in hands or feet, changes in hearing, temporary taste alterations, loss of appetite, diarrhoea and allergic reactions.

Cancer and related diseases are a leading cause of death in today's society. Accordingly there is a strong need to identify new, improved, better and/or alternative pharmaceutical compositions and agents for its treatment, amelioration and prevention. There is a further need for chemotherapeutic agents which address some of the undesirable side effects of known agents. There is also a need for different therapies to be available to physicians to combat the numerous and various types of cancers and to provide new options for treatment to address issues of tolerance of proliferating cells to the existing chemotherapeutic agents and treatment regimes. Agents which can act synergistically with other chemotherapeutics are highly sought after. Any beneficial effects which can be obtained with synergistic agents can reduce the amount and duration of traditional chemotherapeutic drugs, providing safer administration and hopefully fewer or less sever side effects.

It is a preferred object of the present invention to provide pharmaceutical compositions and methods for the treatment, amelioration or prophylaxis of cancer. The present invention also seeks to provide pharmaceutical compositions and methods for targeting neoplastic cells for treatment, which compositions and methods provide improved cell activity in

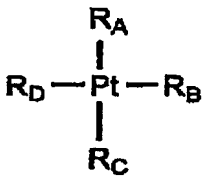
terms of targeting function and/or improved delivery of toxic agents.

Summary of the Invention

This application now describes new therapeutic compositions comprising of platinum-based pharmaceutical agents. The invention is based on the totally unexpected biological activity of new platinum-isoflavanoid complexes and of isoflavones and derivatives thereof which form synergistic compositions with platinum-based chemotherapeutic agents.

The compositions and platinum-isoflavanoid complexes are important targeting agents for the delivery of toxic signals to cells. The compositions and methods of the invention are directed to treating a condition in a mammal, which condition is characterised by the undesirable, detrimental or otherwise unwanted growth or proliferation of cells.

According to an aspect of this invention there is provided platinum-isoflavanoid complexes and analogues thereof described by general formula (I):



(I)

in which

R_A, R_B, R_C, and R_D are independently halo, hydroxy, XR_E, alkoxy, $OC(O)R_F$, $OS(O)R_F$, thio, alkylthio, amino, alkylamino or dialkylamino,

X is O, NR_F or S, and

R_F is hydrogen, alkyl, arylalkyl, alkenyl, aryl or an amino acid,

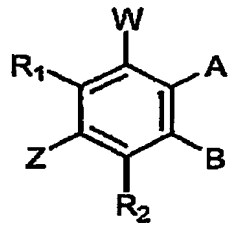
wherein

at least one of R_A, R_B, R_C, and R_D, and preferably only R_A, is XR_E where R_E is an isoflavanoid compound represented by general formula (II) set out below or is derived

from or is a radical or ion of the isoflavanoid compound (II) and ligates to the platinum through any one or more of the heteroatoms X or a radical of the heteroatoms defined as part of R_E or alternatively by a double bond on the isoflavanoid compound (II)

wherein

the isoflavanoid compound is represented by the general formula (II)

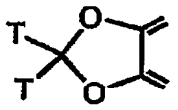


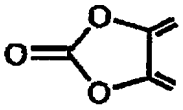
(II)

in which

R_1, R_2 and Z are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, arylalkyl, alkenyl, alkynyl, aryl, heteroaryl, alkylaryl, alkoxyaryl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo, or

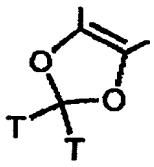
R_2 is as previously defined, and R_1 and Z taken together with the carbon atoms to which they are attached form a five-membered ring selected from

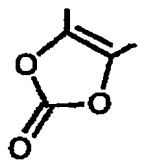




, or

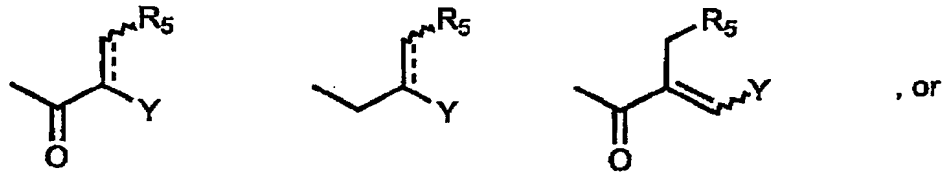
R_1 is as previously defined, and R_2 and Z taken together with the carbon atoms to which they are attached form a five-membered ring selected from





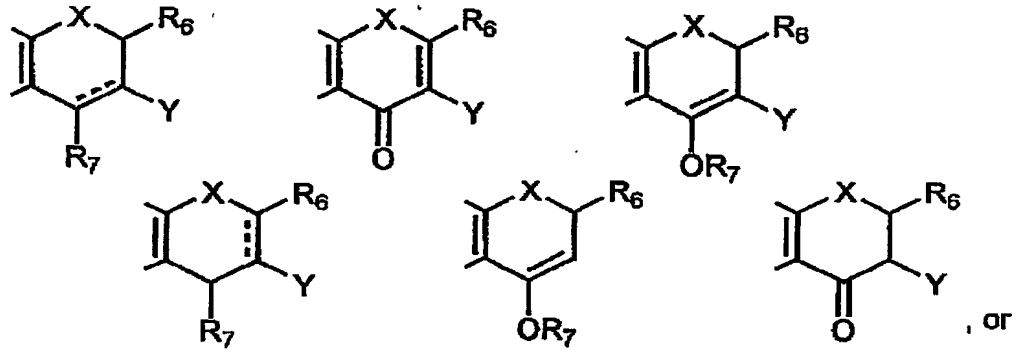
and

W is R_1, A is hydrogen, hydroxy, NR_3R_4 or thio, and B is selected from



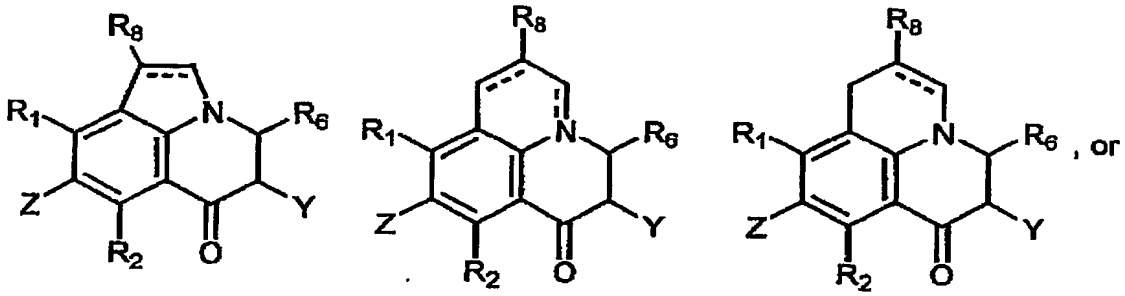
, or

W is R_1, and A and B taken together with the carbon atoms to which they are attached form a six-membered ring selected from



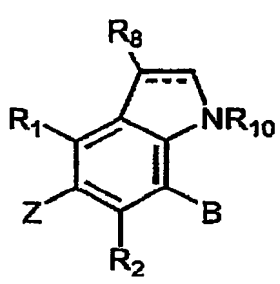
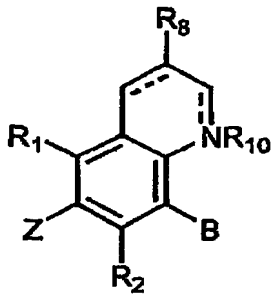
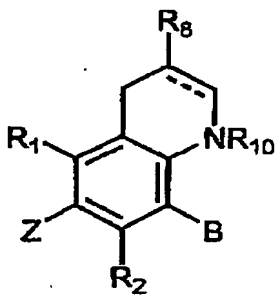
, or

W, A and B taken together with the groups to which they are associated are selected from

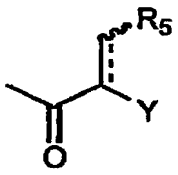
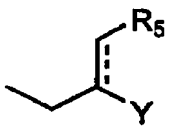
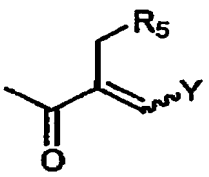


, or

W and A taken together with the groups to which they are associated are selected from

and B is selected from

wherein

R_3 is hydrogen, alkyl, arylalkyl, alkenyl, aryl, an amino acid, $C(O)R_{11}$ where R_{11} is hydrogen, alkyl, aryl, arylalkyl or an amino acid, or CO_2R_{12} where R_{12} is hydrogen, alkyl, haloalkyl, aryl or arylalkyl,

R_4 is hydrogen, alkyl or aryl, or

R_3 and R_4 taken together with the nitrogen to which they are attached comprise pyrrolidinyl or piperidinyl,

R_5 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, or CO_2R_{12} where R_{12} is as previously defined,

R_6 is hydrogen, hydroxy, alkyl, aryl, amino, thio, NR_3R_4, COR_{11} where R_{11} is as previously defined, CO_2R_{12} where R_{12} is as previously defined or $CONR_3R_4$,

R_7 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, alkyl, haloalkyl, alkenyl, aryl, arylalkyl or $Si(R_{13})_3$ where each R_{13} is independently hydrogen, alkyl or aryl,

R_8 is hydrogen, hydroxy, alkoxy or alkyl,

R_9 is alkyl, haloalkyl, aryl, arylalkyl, $C(O)R_{11}$ where R_{11} is as previously defined, or $Si(R_{13})_3$ where R_{13} is as previously defined,

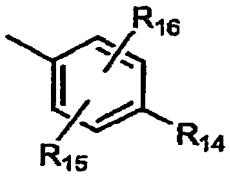
R_{10} is hydrogen, alkyl, haloalkyl, amino, aryl, arylalkyl, an amino acid, alkylamino or dialkylamino,

the drawing "═" represents either a single bond or a double bond,

T is independently hydrogen, alkyl or aryl,

X is O, NR_4 or S, and

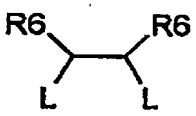
Y is



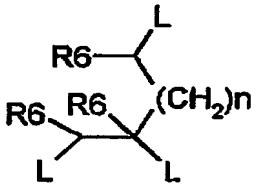
wherein

R_{14}, R_{15} and R_{16} are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, arylalkyl, alkenyl, alkynyl, aryl, heteroaryl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo, or any two of R_{14}, R_{15} and R_{16} are fused together to form a cyclic alkyl, aromatic or heteroaromatic structure, and

when R_A is XR_E, R_B, R_C and/or R_D together may form part of a bidentate or tridentate ligand of general formulae (III) and (IV) respectively



(III)



(IV)

wherein L represents a ligating atom chosen from N, O and S,

n is from 0 to 8, and

each R_6 is independently as defined above or may together form part of a cyclic alkyl, aromatic or heteroaromatic structure,

which platinum-isoflavanoid complexes include pharmaceutically acceptable salts thereof.

It has surprisingly been found by the inventors that platinum-isoflavanoid complexes of the general formula (I) have particular utility and effectiveness in the treatment, prophylaxis, amelioration defence against, and/or prevention of cell proliferation and cancers including benign prostatic hypertrophy; breast cancer; uterine cancer; ovarian cancer; testicular cancer; large bowel cancer; endometrial cancer; prostatic cancer; uterine cancer; and diseases associated with oxidant stress including cancer, myocardial infarction stroke, arthritis, sunlight induced skin damage or cataracts (for convenience hereafter referred to as the "therapeutic indications").

Thus according to an aspect of the present invention there is provided a method for the treatment, prophylaxis, amelioration, defence against, and/or prevention of the therapeutic indications described above which method comprises administering to a subject a therapeutically effective amount of one or more platinum-isoflavanoid complexes of the formula (I) as defined above.

Another aspect of the present invention provides a method of treating a condition in a mammal, which condition is characterised by the undesirable, detrimental or otherwise unwanted growth of cells, said method comprising administering to said mammal an effective amount a platinum-isoflavanoid complex of formula (I) for a time and under conditions sufficient to down-regulate the growth of said cells.

In a preferred embodiment the subject cell growth is proliferation, and the subject down-regulation is killing off the proliferating cells. The condition being treated is preferably cancer, more preferably a metastatic cancer which includes, but is not limited to, breast cancer, prostatic cancer, testicular cancer, ovarian cancer, uterine cancer and/or colorectal cancer.

Another aspect of the present invention provides a method of down-regulating the growth of cells, said method comprising contacting said cells with an effective amount of a platinum-isoflavanoid complex of formula (I).

In a preferred embodiment the subject cell growth is proliferation, and the subject down-regulation is killing off the proliferating cells.

Another aspect of the present invention provides the use of platinum-isoflavanoid complexes of the formula (I) for the manufacture of a medicament for the treatment, amelioration, defence against, prophylaxis and/or prevention of one or more of the therapeutic indications.

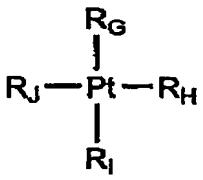
Another aspect of the present invention provides the use of one or more platinum-isoflavanoid complexes of the formula (I) in the treatment, amelioration, defence against, prophylaxis and/or prevention of one or more of the therapeutic indications.

Another aspect of the present invention provides an agent for the treatment, prophylaxis, amelioration, defence against and/or treatment of the therapeutic indications which comprises one or more platinum-isoflavanoid complexes of the formula (I) either alone or in association with one or more carriers or excipients.

Another aspect of the invention provides a therapeutic composition which comprises one or more platinum-isoflavanoid complexes of the formula (I) in association with one or more pharmaceutical carriers and/or excipients.

Another aspect of the present invention provides a drink or food-stuff, which contains one or more platinum-isoflavanoid complexes of the formula (I).

The present invention also provides compositions comprising a platinum complex of the general formula (Ia),



(Ia)

in which

R_G, R_H, R_I, and R_J are independently halo, hydroxy, alkoxy, $OC(O)R_K$, $OS(O)R_K$, thio, alkylthio, amino, alkylamino or dialkylamino,

X is O, NR_K or S, and

R_K is hydrogen, alkyl, arylalkyl, alkenyl, aryl or an amino acid,

or a pharmaceutically acceptable salt thereof,

and an isoflavanoid compound of general formula (II) as defined above.

These compositions comprising a platinum complex of the formula (Ia) and an isoflavanoid compound of the formula (II) are found to have particular utility, effectiveness and synergism in the treatment, prophylaxis, amelioration defence against, and/or prevention of the therapeutic indications set out above.

Thus according to another aspect of the present invention there is provided a method for the treatment, prophylaxis, amelioration, defence against, and/or prevention of the therapeutic indications which comprises administering to a subject a therapeutically effective amount of compositions comprising a platinum complex of the formula (Ia) in conjunction with an isoflavanoid compound of formula (II).

Another aspect of the present invention provides the combined use of a platinum complex of the formula (Ia) and an isoflavanoid compound of the formula (II) in the manufacture of a medicament for the treatment, amelioration, defence against, prophylaxis and/or prevention of the therapeutic indications.

Another aspect of the present invention provides the use of a platinum complex of the formula (Ia) and an isoflavanoid compound of the formula (II) in the treatment, amelioration, defence against, prophylaxis and/or prevention of the therapeutic indications.

Another aspect of the present invention provides a kit comprising a platinum complex of the formula (Ia) and an isoflavanoid compound of the formula (II) either alone or in association with one or more carriers or excipients.

Another aspect of the present invention provides an agent for the treatment, prophylaxis, amelioration, defence against and/or treatment of the therapeutic indications which comprises a composition comprising a platinum complex of the formula (Ia) and an isoflavanoid compound of the formula (II) either alone or in association with one or more carriers or excipients.

Throughout this specification and the claims which follow, unless the text requires otherwise, the word "comprise", and variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

Detailed Description of the Invention

The terms "isoflavanoid" and "isoflavone" as used herein are to be taken broadly to include ring-fused benzopyran molecules having a pendent phenyl group from the pyran ring based on a 1,2-diphenylpropane system. Thus, the classes of compounds generally referred to as isoflavones, isoflavenes, isoflavans, isoflavanones, isoflavanols and the like are generically referred to herein as isoflavones, isoflavone derivatives or isoflavanoid compounds.

The term "alkyl" is taken to mean both straight chain and branched chain alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, secbutyl, tertiary butyl, and the like. The alkyl group has 1 to 10 carbon atoms, preferably from 1 to 6 carbon atoms, more

preferably methyl, ethyl propyl or isopropyl. The alkyl group may optionally be substituted by one or more of fluorine, chlorine, bromine, iodine, carboxyl, C_1-C_4-alkoxycarbonyl, C_1-C_4-alkylamino-carbonyl, di-(C_1-C_4-alkyl)-amino-carbonyl, hydroxyl, C_1-C_4-alkoxy, formyloxy, C_1-C_4-alkyl-carbonyloxy, C_1-C_4-alkylthio, C_3-C_6-cycloalkyl or phenyl.

The term "aryl" is taken to include phenyl and naphthyl and may be optionally substituted by one or more C_1-C_4-alkyl, hydroxy, C_1-C_4-alkoxy, carbonyl, C_1-C_4-alkoxycarbonyl, C_1-C_4-alkylcarbonyloxy or halo.

The term "halo" is taken to include fluoro, chloro, bromo and iodo, preferably fluoro and chloro, more preferably fluoro. Reference to for example "haloalkyl" will include monohalogenated, dihalogenated and up to perhalogenated alkyl groups. Preferred haloalkyl groups are trifluoromethyl and pentafluoroethyl.

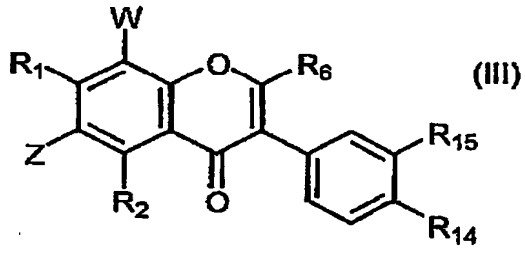
The term "pharmaceutically acceptable salt" refers to an organic or inorganic moiety that carries a charge and that can be administered in association with a pharmaceutical agent, for example, as a counter-cation or counter-anion in a salt. Pharmaceutically acceptable cations are known to those of skilled in the art, and include but are not limited to sodium, potassium, calcium, zinc and quaternary amine. Pharmaceutically acceptable anions are known to those of skill in the art, and include but are not limited to chloride, acetate, citrate, bicarbonate and carbonate.

The term "pharmaceutically acceptable derivative" or "prodrug" refers to a derivative of the active compound that upon administration to the recipient, is capable of providing directly or indirectly, the parent compound or metabolite, or that exhibits activity itself. Prodrugs are included within the scope of the present invention.

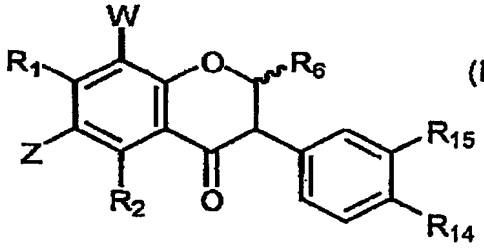
As used herein, the terms "treatment", "prophylaxis" or "prevention", "amelioration" and the like are to be considered in their broadest context. In particular, the term "treatment"

does not necessarily imply that an animal is treated until total recovery. Accordingly, "treatment" includes amelioration of the symptoms or severity of a particular condition or preventing or otherwise reducing the risk of developing a particular condition.

Preferred isoflavanoid compounds of formula (II) are selected from general formulae (III)-(IX):



(III)



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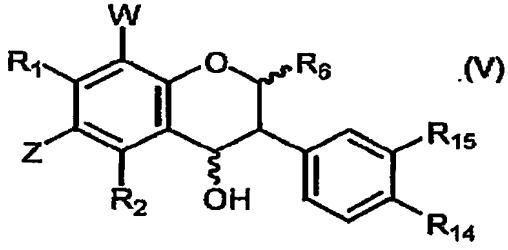

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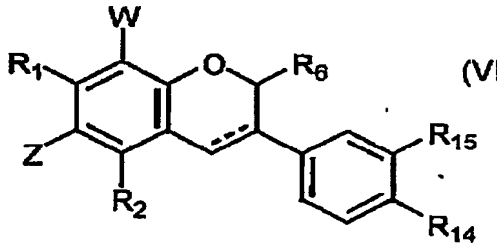

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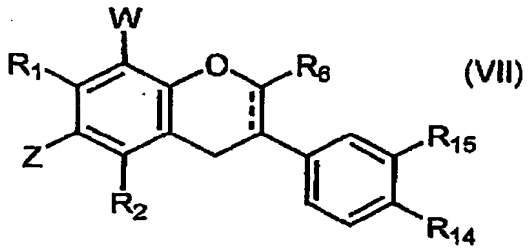

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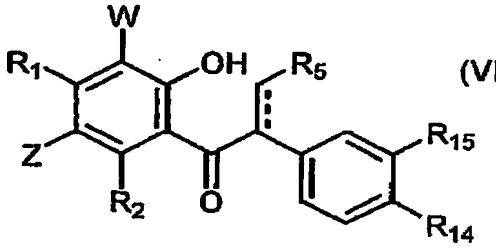
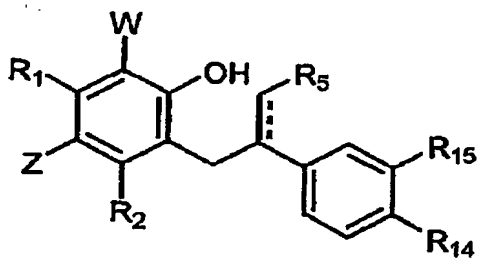


(VIII)



(IX)

in which

R_1, R_2, R_5, R_6, R_{14}, R_{15}, W and Z are as defined above,

more preferably

R_1, R_2, R_{14}, R_{15}, W and Z are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $C(O)R_{10}$, COOH, CO_2R_{10}, alkyl, haloalkyl, arylalkyl, aryl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo,

R_5 is hydrogen, $C(O)R_{11}$ where R_{11} is hydrogen, alkyl, aryl, or an amino acid, or CO_2R_{12} where R_{12} is hydrogen, alkyl or aryl,

R_6 is hydrogen, hydroxy, alkyl, aryl, COR_{11} where R_{11} is as previously defined, or CO_2R_{12} where R_{12} is as previously defined,

R_9 is alkyl, haloalkyl, arylalkyl, or $C(O)R_{11}$ where R_{11} is as previously defined, and

R_{10} is hydrogen, alkyl, amino, aryl, an amino acid, alkylamino or dialkylamino,

more preferably

R_1 and R_{14} are independently hydroxy, OR_9, $OC(O)R_{10}$ or halo,

R_2, R_{15}, W and Z are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $C(O)R_{10}$, COOH, CO_2R_{10}, alkyl, haloalkyl, or halo,

R_5 is hydrogen, $C(O)R_{11}$ where R_{11} is hydrogen or alkyl, or CO_2R_{12} where R_{12} is hydrogen or alkyl,

R_6 is hydrogen or hydroxy,

R_9 is alkyl, arylalkyl or $C(O)R_{11}$ where R_{11} is as previously defined, and

R_{10} is hydrogen or alkyl,

and more preferably

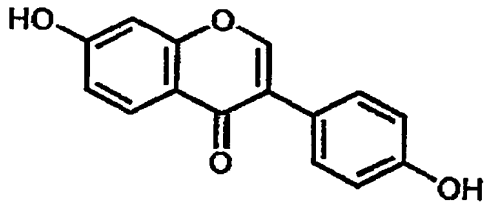
R_1 and R_{14} are independently hydroxy, methoxy, benzyloxy, acetyloxy or chloro,

R_2, R_{15}, W and Z are independently hydrogen, hydroxy, methoxy, benzyloxy, acetyloxy, methyl, trifluoromethyl or chloro,

R_5 is hydrogen or CO_2R_{12} where R_{12} is hydrogen or methyl, and

R_6 is hydrogen.

Particularly preferred isoflavanoid compounds of formula (II) are selected from:



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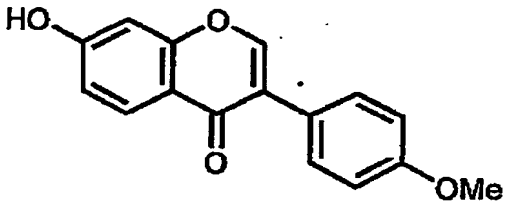

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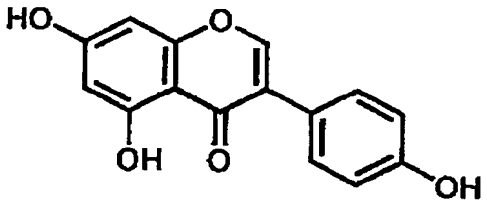

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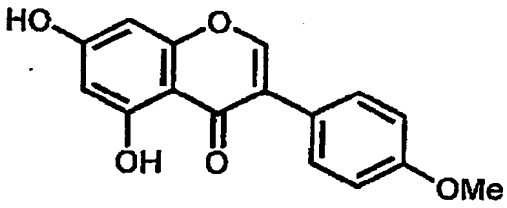

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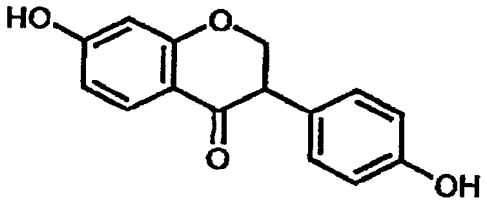

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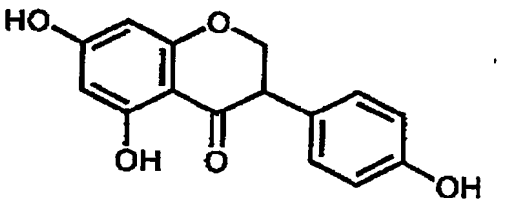

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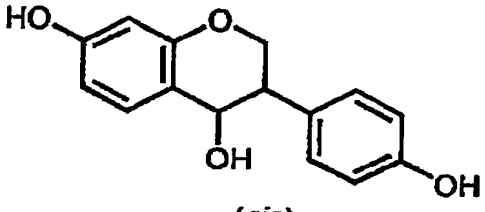

(*cis*)

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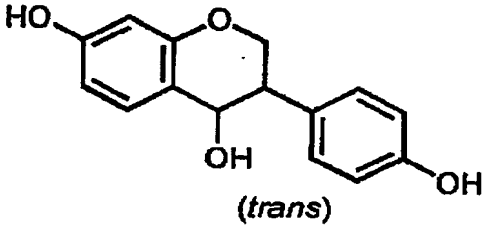

(*trans*)

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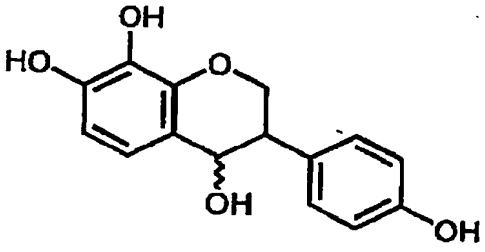

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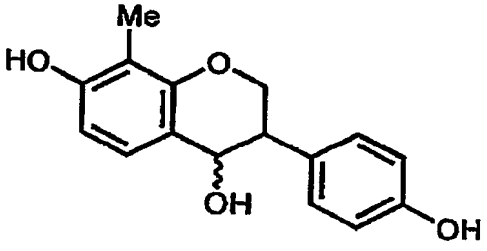

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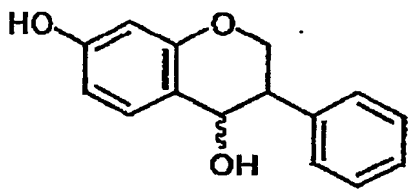

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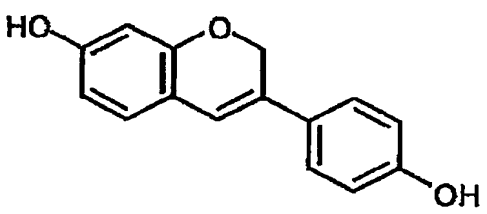

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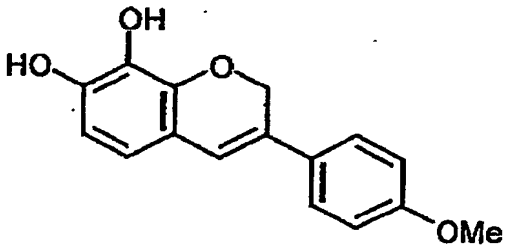

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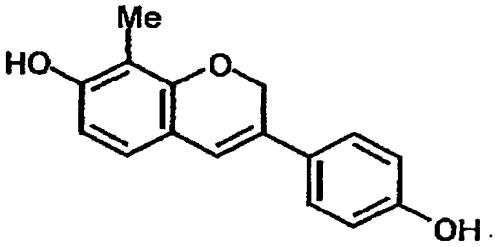

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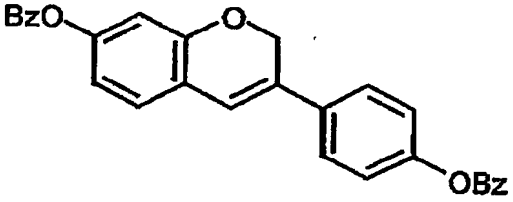

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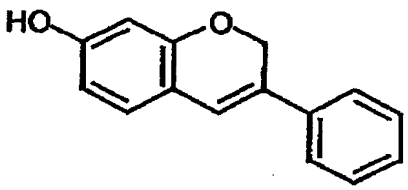

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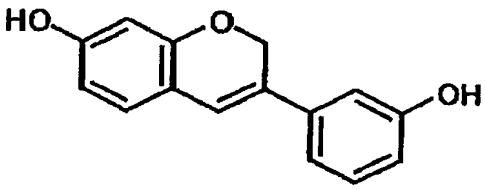

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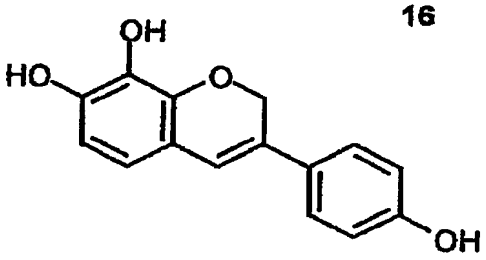

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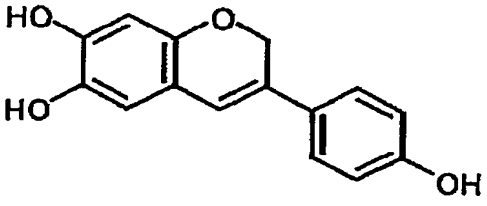

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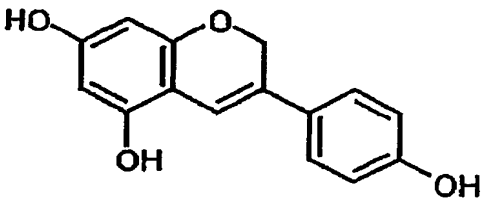

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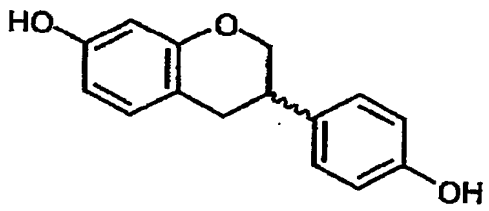

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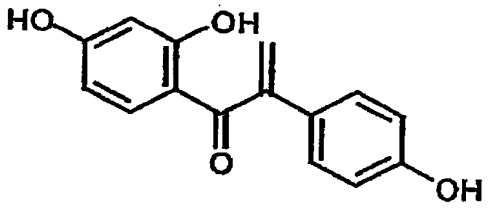

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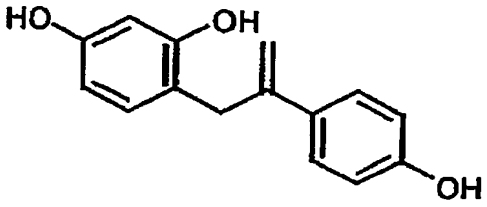

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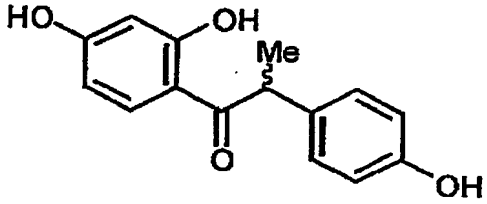

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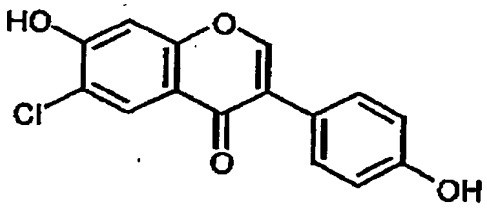

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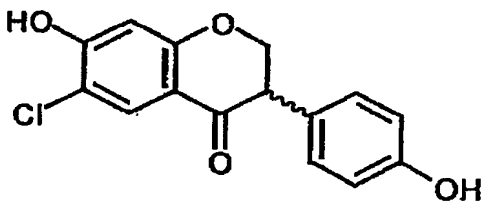

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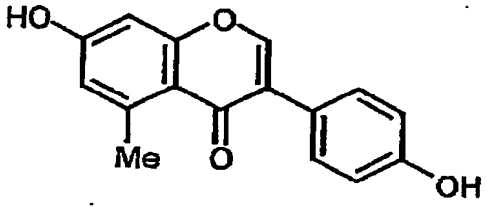

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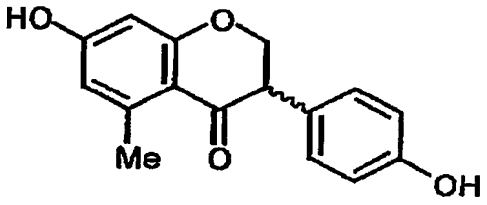

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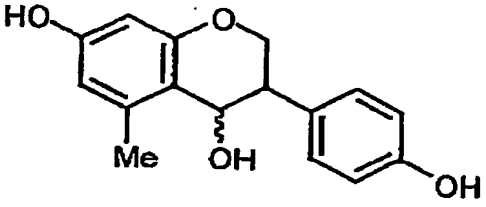

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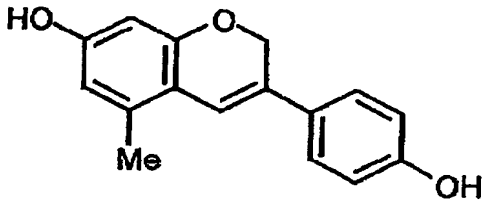


30

Preferred bidentate and tridentate platinum ligands of the present invention include those commonly known in the art. For example, suitable bidentate ligands may be selected from ethylene-1,2-diamine and 1,10-phenathraline and other ligands well known in the art.

Preferred platinum complexes are halo and amino substituted, more preferably chloro and amine substituted, more preferably *cis*-dichlorodiamino substituted. Preferred platinum-isoflavanoid complexes are preferably halo and amino substituted, more preferably *cis*-dichloroamino substituted or *cis*-diaminochloro substituted.

Compounds of the present invention have particular application in the treatment of diseases associated with or resulting from estrogenic effects, androgenic effects, vasolidatory and spasmodic effects, inflammatory effects and oxidative effects.

The amount of compounds of formulae I or Ia and II which are required in a therapeutic treatment according to the invention will depend upon a number of factors, which include the specific application, the nature of the particular compound used, the condition being treated, the mode of administration and the condition of the patient. Compounds of formulae I or Ia and II may be administered in a manner and amount as is conventionally practised. See, for example, Goodman and Gilman, *The Pharmacological Basis of Therapeutics*, 1299 (7th Edition, 1985). The specific dosage utilised will depend upon the condition being treated, the state of the subject, the route of administration and other well known factors as indicated above. In general, a daily dose per patient may be in the range of 0.1 mg to 10 g; typically from 0.5 mg to 1 g; preferably from 50 mg to 200 mg. Importantly the synergistic relationship of compounds of general formula I or Ia and II allow for significant reductions in dosage regimes of relatively toxic drugs such as cisplatin.

The production of a pharmaceutical composition for the treatment of the therapeutic indications herein described (for convenience hereafter referred to as the "active

compounds") are typically admixed with one or more pharmaceutically or veterinarially acceptable carriers and/or excipients as are well known in the art.

The carrier must, of course, be acceptable in the sense of being compatible with any other ingredients in the formulation and must not be deleterious to the subject. The carrier or excipient may be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose, for example, a tablet, which may contain from 0.5% to 59% by weight of the active compound, or up to 100% by weight of the active compound. One or more active compounds may be incorporated in the formulations of the invention, which may be prepared by any of the well known techniques of pharmacy consisting essentially of admixing the components, optionally including one or more accessory ingredients.

The formulations of the invention include those suitable for oral, rectal, optical, buccal (for example, sublingual), parenteral (for example, subcutaneous, intramuscular, intradermal, or intravenous) and transdermal administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular active compound which is being used.

Formulation suitable for oral administration may be presented in discrete units, such as capsules, sachets, lozenges, or tablets, each containing a predetermined amount of the active compound; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. Such formulations may be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound and a suitable carrier (which may contain one or more accessory ingredients as noted above). In general, the formulations of the invention are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the resulting mixture such as to form a unit dosage. For example, a tablet may be prepared by compressing or moulding a powder or granules containing the active compound, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a

suitable machine, the compound of the free-flowing, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent, and/or surface active/dispersing agent(s). Moulded tablets may be made by moulding, in a suitable machine, the powdered compound moistened with an inert liquid binder.

Formulations suitable for buccal (sublingual) administration include lozenges comprising the active compound in a flavoured base, usually sucrose and acacia or tragacanth; and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

Compositions of the present invention suitable for parenteral administration conveniently comprise sterile aqueous preparations of the active compounds, which preparations are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also be effected by means of subcutaneous, intramuscular, or intradermal injection. Such preparations may conveniently be prepared by admixing the compound with water or a glycine buffer and rendering the resulting solution sterile and isotonic with the blood. Injectable formulations according to the invention generally contain from 0.1% to 60% w/v of active compound(s) and are administered at a rate of 0.1 ml/minute/kg or as appropriate. Parenteral administration is a preferred route of administration for the compounds of the present invention.

Formulations suitable for rectal administration are preferably presented as unit dose suppositories. These may be prepared by admixing the active compound with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

Formulations or compositions suitable for topical administration to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used include Vaseline, lanoline, polyethylene glycols, alcohols, and combination

of two or more thereof. The active compound is generally present at a concentration of from 0.1% to 0.5% w/w, for example, from 0.5% to 2% w/w. Examples of such compositions include cosmetic skin creams.

Formulations suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain the active compound as an optionally buffered aqueous solution of, for example, 0.1 M to 0.2 M concentration with respect to the said active compound.

Formulations suitable for transdermal administration may also be delivered by iontophoresis (see, for example, *Pharmaceutical Research 3* (6), 318 (1986)) and typically take the form of an optionally buffered aqueous solution of the active compound. Suitable formulations comprise citrate or bis/tris buffer (pH 6) or ethanol/water and contain from 0.1 M to 0.2 M active ingredient.

The active compounds may be provided in the form of food stuffs, such as being added to, admixed into, coated, combined or otherwise added to a food stuff. The term food stuff is used in its widest possible sense and includes liquid formulations such as drinks including dairy products and other foods, such as health bars, desserts, etc. Food formulations containing compounds of the invention can be readily prepared according to standard practices.

Therapeutic methods, uses and compositions may be for administration to humans or animals, including mammals such as companion and domestic animals (such as dogs and cats) and livestock animals (such as cattle, sheep, pigs and goats), birds (such as chickens, turkeys, ducks) and the like.

The active compound or pharmaceutically acceptable derivatives prodrugs or salts thereof can also be co-administered with other active materials that do not impair the desired

action, or with materials that supplement the desired action, such as antibiotics, antifungals, antiinflammatories, or antiviral compounds. The active agent can comprise two or more isoflavones or derivatives thereof in combination or synergistic mixture. The active compounds can also be administered with lipid lowering agents such as probucol and nicotinic acid; platelet aggregation inhibitors such as aspirin; antithrombotic agents such as coumadin; calcium channel blockers such as verapamil, diltiazem, and nifedipine; angiotensin converting enzyme (ACE) inhibitors such as captopril and enalapril, and □-blockers such as propanolol, terbutalol, and labetalol. The compounds can also be administered in combination with nonsteriodal antiinflammatories such as ibuprofen, indomethacin, aspirin, fenoprofen, mefenamic acid, flufenamic acid and sulindac. The compounds can also be administered with corticosteroids.

The co-administration may be simultaneous or sequential. Simultaneous administration may be effected by the compounds being in the same unit dose, or in individual and discrete unit doses administered at the same or similar time. Sequential administration may be in any order as required and typically will require an ongoing physiological effect of the first or initial active agent to be current when the second or later active agent is administered, especially where a cumulative or synergistic effect is desired.

The isoflavones of formula (II) for use in the present invention may be derived from any number of sources readily identifiable to a person skilled in the art. Preferably, they are obtained in the form of concentrates or extracts from plant sources. Again, those skilled in the art will readily be able to identify suitable plant species, however, for example, plants of particular use in the invention include leguminous plants. More preferably, the isoflavone extract is obtained from chickpea, lentils, beans, red clover or subterranean clover species and the like.

Isoflavone extracts may be prepared by any number of techniques known in the art. For example, suitable isoflavone extracts may be prepared by water/organic solvent extraction from the plant source. It will be appreciated that an isoflavone extract may be prepared

from any single tissue of a single species of plant or a combination of two or more different tissues thereof. Similarly, an extract may be prepared from a starting material which contains a heterogeneous mixture of tissues from two or more different species of plant.

Generally, where an isoflavone extract is prepared from plant material, the material may be comminuted or chopped into smaller pieces, partially comminuted or chopped into smaller pieces and contacted with water and an organic solvent, such as a water miscible organic solvent. Alternatively, the plant material is contacted with water and an organic solvent without any pre-treatment. The ratio of water to organic solvent may be generally in the range of 1:10 to 10:1 and may, for example, comprise equal proportions of water and solvent, or from 1% to 30% (v/v) organic solvent. Any organic solvent or a mixture of such solvents may be used. The organic solvent may preferably be a C2-10, more preferably a C1-4 organic solvent (such as methanol, chloroform, ethanol, propanol, propylene glycol, erythrite, butanol, butanediol, acetonitrile, ethylene glycol, ethyl acetate, glycidol, glycerol dihydroxyacetone or acetone). Optionally the water/organic solvent mixture may include an enzyme which cleaves isoflavone glycosides to the aglycone form. The mixture may be vigorously agitated so as to form an emulsion. The temperature of the mix may range, for example, from an ambient temperature to boiling temperature. Exposure time may be between one hour to several weeks. One convenient extraction period is twenty-four hours at 90°C. The extract may be separated from undissolved plant material and the organic solvent removed, such as by distillation, rotary evaporation, or other standard procedures for solvent removal. The resultant extract containing water soluble and non-water soluble components may be dried to give an isoflavone-containing extract, which may be formulated with one or more pharmaceutically acceptable carriers, excipients and/or auxiliaries according to the invention.

An extract made according to the description provided in the previous paragraphs may contain small amounts of oil which include isoflavones in their aglycone form (referred to herein as isoflavones). This isoflavone enriched oil, may be subject to HPLC to adjust the

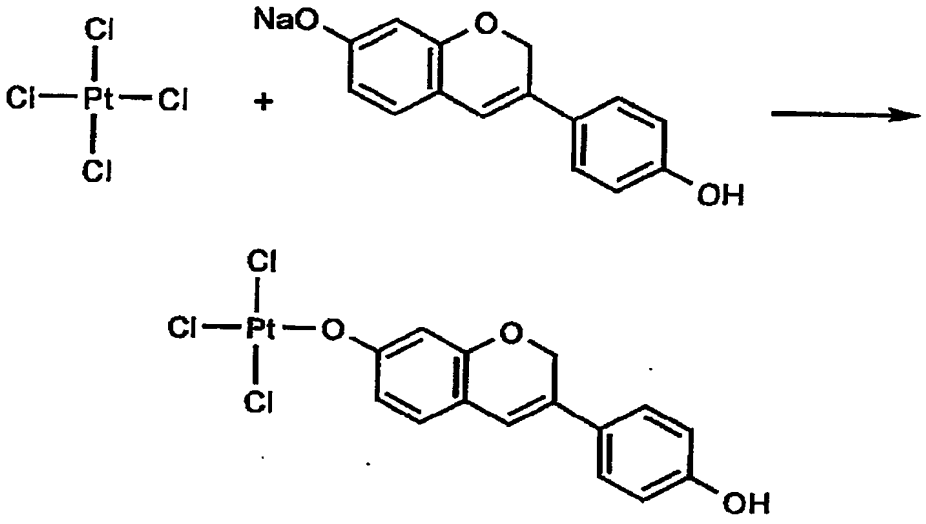
isoflavone ratios, or, if it is at the desired isoflavone ratio, may be dried, for example in the presence of silica, and be formulated with one or more carriers, excipients and/or auxiliaries to give an isoflavone containing extract. Alternatively, the isoflavones contained in said small amounts of oil may be further concentrated by addition to the oil of a non-water soluble organic solvent such as hexane, heptane, octane acetone or a mixture of one or more of such solvents. One example is 80% hexane, 20% acetone w/w having high solubility for oils but low solubility for isoflavones. The oil readily partitions into the organic solvent, and an enriched isoflavone containing extract falls out of solution. The recovered extract may be dried, for example in an oven at 50°C to about 120°C, and formulated with one or more pharmaceutically acceptable carriers, excipients and/or auxiliaries.

It will be appreciated that the present invention also contemplates the production of suitable isoflavones, functional derivatives, equivalents or analogues thereof, by established synthetic techniques well known in the art. See, for example, Chang *et al.* (1994) which discloses methods appropriate for the synthesis of various isoflavones.

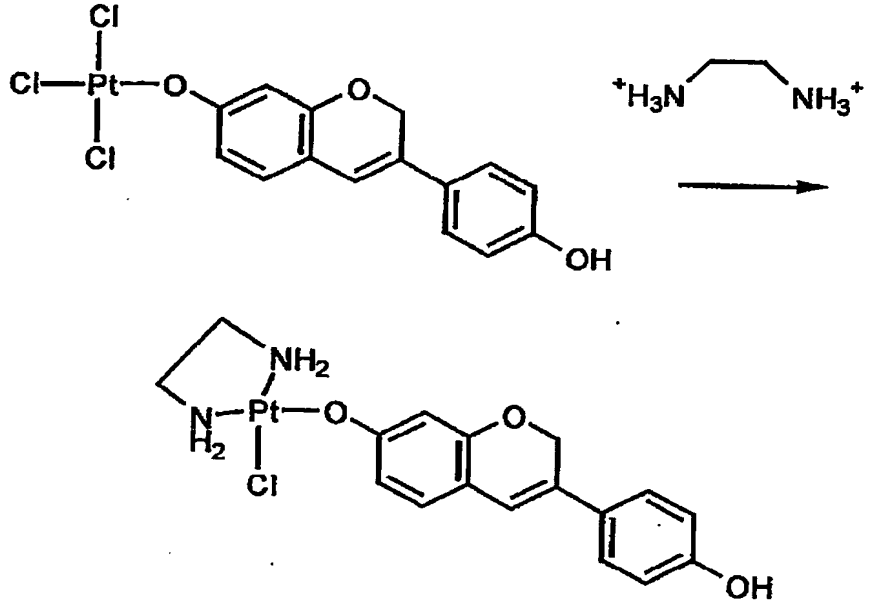
International Patent Applications WO 98/08503 and WO 00/49009 (which are incorporated herein in their entirety by reference) and references cited therein also provide general synthetic methods for the preparation of isoflavanoid compounds for use in the present invention.

General methods known in the art may also be employed by those skilled in the art of chemical synthesis for constructing the platinum complexes depicted in formula (I), and by reference to the general schemes 1 and 2 below.

Chemical functional group protection, deprotection, synthons and other techniques known to those skilled in the art may be used where appropriate in the synthesis of the compounds of the present invention.



Scheme 1



Scheme 2

The invention is further described with reference to the following non-limiting examples.

Example 1

The effect of a composition comprising the platinum complex cisplatin and the isoflavanoid compound dehydroequol (compound No. 12) on cancer cell line A2780 is assessed on culture plates. It is found that the composition comprising the platinum complex and the isoflavanoid compound exhibits good chemotherapeutic properties. The amount of cisplatin needed to kill a set number of cancer cells is less when in admixture with an isoflavanoid compound of the present invention as compared to a control with cisplatin alone. This example demonstrates the surprising synergy between cisplatin and the isoflavanoid compounds of the present invention.

Example 2

Equally surprising results with cancer cell line A2780 are seen with the platinum-isoflavanoid complex of the invention depicted in Scheme 2 above.

These examples highlight the utility of the compounds of formula (I) and of the composition of compounds of formulae (Ia) and (II) as therapeutic agents for the down regulation of cell proliferation and the treatment, amelioration, defence against, prophylaxis and/or prevention of the therapeutic indications.

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The inventions also includes all of the steps, features, compositions and compounds referred to or indicated in the specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that that prior art forms part of the common general knowledge in the field of endeavour.

Dated this 2nd day of October 2002
Novogen Research Pty Limited

by its Patent Attorneys
Davies Collison Cave